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Appellants:	Peter M. Glazer and Pamela Havre		
Serial No.:	09/783,338	Art Unit:	1634
Filed:	February 14, 2001	Examiner:	Jeffrey Norman Fredman

For: *"CHEMICALLY MODIFIED OLIGONUCLEOTIDE FOR SITE-DIRECTED MUTAGENESIS"*

ATL1 #574974 v1

PTO/SB/21 (01-03)
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Application Number	09/783,338
Filing Date	February 14, 2001
First Named Inventor	Peter M. Glazer
Art Unit	1634
Examiner Name	Jeffrey Norman Fredman
Attorney Docket Number	YU 109 CON

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
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☑ Applicant claims small entity status. See 37 CFR 1.27

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Application Number	09/783,338
Filing Date	February 14, 2001
First Named Inventor	Peter M. Glazer
Examiner Name	Jeffrey Norman Fredman
Art Unit	1634
Attorney Docket No.	YU 109 CON

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1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

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			Extra Claims		Fee from below	=	Fee Paid
Total Claims	9	-20	0	x	0	=	0
Independent Claims	1	- 3** =	0	x	0	=	0
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
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1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
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Name (Print/Type)	Patrea L. Pabst	*Registration No. (Attorney/Agent)*	31,284	*Telephone*	(404) 817-8528
Signature				*Date*	September 11, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Peter M. Glazer and Pamela Havre

Serial No.: 09/783,338 Art Unit: 1634

Filed: February 14, 2001 Examiner: Jeffrey Norman Fredman

For: *"CHEMICALLY MODIFIED OLIGONUCLEOTIDE FOR SITE-DIRECTED MUTAGENESIS"*

Assistant Commissioner for Patents
Washington, D.C. 20231

REPLY BRIEF

Sir:

This is a Brief in reply to the Examiner's Answer mailed August 8, 2003. A Request for Oral Hearing accompanies this Reply along with the appropriate fee of $140.00. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

Response to Examiner's Arguments

The Appellants agree with the Examiner in that the central issue on Appeal is the whether the claims, as they relate to *in vivo* gene therapy, lack enablement.

Appellants maintain that the present invention is properly supported and enabled by the specification. First, the specification contains several examples showing that site-specific mutagenesis is achieved not only in cell-free systems but in mammalian cells as well (COS and

fibroblast cells). Second, the Declaration by Dr. Glazer ("Declaration") demonstrates that such *in vitro* examples (as characterized by the examiner) are predictive of efficacy *in vivo* in animals for triplex forming oligonucleotides.

(i) The art is predictable

The Examiner appears to agree that the information provided in Example 1 of the specification, wherein a triplex forming oligonucleotide linked to psoralen was used to achieve site-specific, targeted mutagenesis in a specific gene in an intact, double-stranded lambda phage genome, is accurate. However, at the same time, the Examiner references prior art that includes unsupported statements that triplex forming oligonucleotides designed to block transcription and even antisense oligos, meant to prevent translation, may have unintended and unexpected mutagenic effects (see Examiner's Answer, page 15).

First, the legal standard for patentability is not that the claimed method cannot have some possible negative consequences, but whether or not it will work for its intended purpose. All the evidence presented by appellants clearly demonstrates that the claimed oligonucleotides do induce site-specific mutations in the intended target. The examiner has presented no evidence to the contrary, only the observation, typical of scientific publications, that there might be some adverse consequences.

Second, the claimed method relates to using triplex forming oligonucleotides, linked to a mutagen, to achieve site-specific targeted mutagenesis. Oligonucleotides designed to block transcription and/or translation are a completely separate technology/issue. Antisense oligonucleotides *shown to prevent transcription or translation* certainly would not allow for

replication of the target sequence. Such oligonucleotides are completely different from the oligonucleotides defined by claimed method (see page 17, Example 1, wherein the phage particles were adsorbed to *E. coli* and ***grown as individual plaques*** to allow genetic analyses of the *supF* and *cI* genes; and wherein "[P]hotoactivation of the psoralen generated a DNA adduct, and *in vitro* packaging of the psoralen-AG10. The lambda *supF* DNA complex ***allowed growth of the phage in bacteria*** to fix the adduct into a mutation. ***The phage particles were grown as individual plaques on a bacterial lawn to detect targeted mutagenesis***..." [emphasis added to show *in vivo* aspect of the example]). One of ordinary skill in the art will realize that in order for phage particles to grow/multiply, *in vivo* replication of DNA and *in vivo* gene expression is essential. In the present case, *replication is actually required to fix the adduct into a mutation.* Furthermore, gene expression produces the proteins that are the building blocks for the structural phage particles (i.e. phage coat proteins). Therefore, the specification, and the data therein, directly refutes the Examiner's assertions that triplexes on DNA that replicated following transfection are less stable ..." (see sentence bridging pages 6 and 7 of the Examiner's answer).

The Examiner further refers to references that allegedly assert a lack of understanding the precise role of nucleases and other intracellular enzymes and proteins on the stability of *ribozymes* (see page 6 of the Examiner's Answer). Appellants are unsure as to where/how ribozymes apply to an analysis of the present invention, however, as presented throughout the specification and Declaration, many examples are provided wherein triplex forming oligonucleotides (with and without mutagen) bind to target DNA in the cellular compartment of the nucleus. One of ordinary skill in the art will realize that, in view of the results discussed

therein, the triplex forming oligonucleotides traversed the cytoplasmic milieu of cell (from cell exterior, across cell membrane, through the cytoplasm, across the nuclear membrane) without significant "harm" from nucleases or proteins/enzymes (which are housed in the very compartments in which the oligonucleotide must pass on its way to the DNA target). This is even eluded to at page 4 of the Declaration, wherein "[T]he importance of this result is to establish the concept that DNA binding molecules can be used to direct site-specific genome modification and to show that the cell and nuclear membranes and the packaging of the DNA into chromatin are not absolute barriers to gene targeting the antigene oligonucleotides."

While the Examiner has credited the Declaration with demonstrating substantial uptake of triplex forming oligonucleotides, it appears that he has disregarded the *in vivo* data centering on site-specific, triplex forming oligonucleotide-directed genome modification in intact animals, thereby resulting in heritable changes in gene function and expression (see page 7 of the Declaration); further *in vivo* data centering on evidence that AG30-mediated mutation induction occurs through a sequence-specific, triplex-mediated mechanism, and that "nonspecific oligonucleotides are not generally mutagenic in animals" (see page 10, lines 3-5, of the Declaration); and previous studies (cited in the Declaration at page 13) indicating that "small DNA molecules can be administered by i.p. or intravenous injections and gain access to tissues (outside the central nervous system) and to cell nuclei." Furthermore, the Declaration makes it clear that the work described therein demonstrates that chromosomal DNA throughout the somatic tissues of an animal can be targeted by nucleic acids (see page 13 of the Declaration).

The Examiner asserts at page 11 of the Examiner's Answer, that "[S]imply correcting a few cells of the arbitrary mutation created in the mouse is not enough for patentable use." The appellants are claiming methods of mutating double stranded nucleic acid molecules using mutagenic oligonucleotides. Nowhere in the claims is there a recitation/limitation that requires therapeutic efficacy or mutation of genes in all cells. Furthermore, there is no requirement that one must ask, "why should one have to show that '32 mutants out of 144,768 cells have an effect on the metabolism of an animal', if the claims are simply directed to mutating a double stranded nucleic acid molecule? (see page 12, lines 2-4 of the Examiner's Answer). Indeed, even if there were such a requirement, subsequent studies have shown that less than 2% transformation of the genes is sufficient to confer a therapeutic effect.

The examiner discounts the evidence provided in the Declaration on the grounds that the oligonucleotides in the animal study do not include a mutagen. However, there has been no evidence provided by the examiner that the evidence in the Declaration would not be predictive of an oligonucleotide which further included a small molecule mutagen such as a psoralen. The evidence in the Declaration clearly demonstrated efficacy in a cell system which was predictive of the actual efficacy in animals. Appellants have provided similar results for the oligonucleotides bound to a mutagen using both cell-free and cell systems. Absent some evidence otherwise, one skilled in the art would expect the oligonucleotides bound to a mutagen to have the same degree of efficacy in animals as in the cell systems, based on the evidence in the Declaration.

(9) SUMMARY AND CONCLUSION

It is well established that the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 321, 325 (CCPA 1956). However, in this case, numerous actual examples have been provided which fully support the claimed method. The specification, in *combination* with information known in the art at the time of filing, clearly enables one skilled in the art to practice the claimed method, with a reasonable expectation of success. This expectation of success if further supported by the information provided in the Declaration:

1) The *in vivo* data presented in the Declaration showed site-specific, triplex forming oligonucleotide-directed genome modification in intact animals, thereby resulting in heritable changes in gene function and expression (see page 7 of the Declaration);

2) The *in vivo* data presented in the Declaration showed that AG30-mediated mutation induction occurs through a sequence-specific, triplex-mediated mechanism, and that "nonspecific oligonucleotides are not generally mutagenic in animals" (see page 10, lines 3-5, of the Declaration);

3) Previous studies (cited in the Declaration at page 13) indicate that "small DNA molecules can be administered by i.p. or intravenous injections and gain access to tissues (outside the central nervous system) and to cell nuclei." Furthermore, the Declaration makes it clear that the work described therein demonstrates that chromosomal DNA throughout the somatic tissues of an animal can be targeted by nucleic acids (see page 13 of the Declaration);

4) The specification's disclosure of triplex forming oligonucleotides linked to psoralen, targeting mutagenesis in a specific gene in an intact, double stranded lambda phage genome (see Example 1 of the specification). Importantly, while photoactivation of the psoralen generated a DNA adduct and *in vitro* packaging of the psoralen linked oligonucleotide was likely done *in vitro*, the psoralen-linked oligonucleotide complexed to DNA allowed ***growth of the phage in bacteria*** to fix the adduct into a mutation. The phage particles ***were subsequently grown as individual plaques on a bacterial lawn*** (see page 17 of the specification). Again, this data supports the appellants contention that a mutagen incorporated into a single-stranded nucleic acid, does **NOT** inhibit common, essential enzymatic activities present *in vivo* (i.e. those activities associated with DNA replication, required for phage replication, and gene expression, required for the production of phage coat proteins). These activities are present within the intact bacterial cell, *as well as in any intact cell, whether it is a eukaryotic cell or prokaryotic cell (and are exemplified in the specification's teaching of COS cells and mouse fibroblast systems)*; and

5) The general resistance of oligonucleotides, unlinked and linked to a mutagen, to metabolic breakdown, nuclease activity, or other activity which may "disturb" the oligonucleotide before it reaches its final destination, the DNA target sequence. Such evidence is provided in the specification and in the Declaration, wherein the triplex forming oligonucleotides traversed the cytoplasmic milieu of cell (from cell exterior, across cell membrane, through the cytoplasm, across the nuclear membrane) without significant "harm" from nucleases or proteins/enzymes (which are housed in the very compartments in which the oligonucleotide must pass on its way to the DNA target).

For the foregoing reasons, Appellants submit that the claims 6-14 are patentable.

Respectfully submitted,

Patrea L. Pabst
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Date: September 11, 2003

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Peggy Bailey

Date: September 11, 2003

ATL1 #592316 v1